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An Improved Synthesis of [^{15}N] Labelled Acetamide and Acetonitrile

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Summary

An improved synthesis of [^{15}N] labelled acetamide and acetonitrile is described which provides these compounds in yields of 85% and 64%, respectively. The key difference in the present preparation is the use of 2,2,2-trifluoroethyl acetate for the reaction with $^{15}NH_4OH$.

Key Words: ^{15}N, acetonitrile, acetamide

Introduction

The preparation of ^{15}N labelled acetonitrile has usually been achieved by one of the three procedures outlined below:

$$CH_3I + KCN^*/NaCN^* \rightarrow CH_3CN^* \tag{1}$$

$$(CH_3)_2SO_4 + KCN^* \rightarrow CH_3CN^* \tag{2}$$

$$(CH_3CO)_2O + {}^*NH_3 \rightarrow CH_3CO\overset{*}{N}H_2 \tag{3}$$

$$CH_3CO\overset{*}{N}H_2 \xrightarrow{P_2O_5} CH_3C\overset{*}{N} \tag{4}$$

Scheme 1

The first reaction in Scheme 1 provides $CH_3C^{15}N$ in a high yield (88-95%), but suffers from the use of relatively expensive $KC^{15}N$ and/or $NaC^{15}N$.[1,2] The second procedure (dimethyl sulfate)[3] also employs $KC^{15}N$ but does not appear to provide any inherent advantage (lower yield ~67%) over the classic approach represented by reaction 1. The third approach has the advantage of starting with relatively inexpensive $^{15}NH_3$ (or $^{15}NH_4Cl$), but is a two-step reaction (3 and 4) which has a poor overall yield (34-47%).[4,5] Nevertheless, the simplicity of the second step dehydration (P_2O_5) makes this approach attractive, if the overall yield could be improved.

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Our synthetic strategy was based on the classic ammonolysis reaction of ethyl acetate.[6] Unfortunately, good yields in this reaction are usually obtained with a large excess of ammonia. An alternative approach is to employ an ester with a better leaving group (e.g. 2,2,2-trifluoroethyl acetate). In addition, the alcohol 2,2,2-trifluoroethanol liberated during the ammonolysis reaction has a relatively low boiling point and can be readily removed by simple distillation. Subsequent dehydration of $CH_3\ CO^{15}N_2$ by heating in the presence of (P_2O_5) provides $CH_3C^{15}N$.

$$CH_3COOCH_2CF_3 + {}^{15}NH_4OH \xrightarrow{\Delta} CH_3CO^{15}NH_2 + CF_3CH_2OH + H_2O \qquad (5)$$

$$CH_3CO^{15}NH_2 \xrightarrow{P_2O_5} CH_3C^{15}N \qquad (6)$$

Based on several experiments, the yield for the first step was ~85% and the subsequent dehydration step provides a yield of 75% (i.e., overall yield of 64%). Thus, the present procedure appears to be competitive with previous procedures.

Experimental

The ^1H NMR data were obtained using a Bruker WP/200 instruments. The 2,2,2-trifluoroethyl acetate sample was prepared from acetic anhydride (Aldrich Chemical Co.) and 2,2,2-trifluoroethanol (Aldrich Chemical Co.) in the presence of pyridine. The labelled (99%) $^{15}NH_3$ was obtained from Isotec, Inc. The concentrated (28%) $^{15}NH_4OH$ solution was prepared by bubbling $^{15}NH_3$ gas into deionized water at ~5°C.

Synthesis of ^{15}N Labelled Acetamide

A concentrated solution of $^{15}NH_4OH$ (28% $^{15}NH_3$, 6.5 ml ~ 97 mmol) was quickly added to 15.5 g (109 mmol) of 2,2,2-trifluoroethyl acetate which was precooled in an ice bath. The mixture initially formed two distinct transparent layers and was allowed to warm to room temperature. The mixture was subsequently stirred overnight at room temperature. The clear homogeneous mixture was distilled with an organic fraction distilling at 70-90°C and an aqueous phase distilling at 90-109°C. The remaining liquid in the distillation pot was placed in a desiccator and crystalline ^{15}N acetamide slowly formed upon cooling. The yield was 5 g (85% yield) with a m.p. 81.5-82°C, lit. 82.3°C. The ^{15}N $CH_3CO^{15}NH_2$ was pure as indicated by ^1H NMR analysis, ^1H NMR, ($CDCl_3$) δ 2.01(s) 3H; 5.75(d)2H, ($^1J_{NH}$ = 88 Hz).

Synthesis of ^{15}N Labelled Acetonitrile

In a 25 ml round bottom flask equipped with a short path distillation column was placed 8 g (0.056 moles) of P_2O_5 and 5 g (0.083 moles) of $CH_3CO^{15}NH_2$. The mixture was slowly heated and the fraction distilling at ~81°C was collected. The yield of $CH_3C^{15}N$ was 2.6 g (75% yield). The ^1H NMR (CCl_4) δ 1.97, (d) 3H, ($^3J_{NH}$=1.8 Hz).

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